AstraZeneca	AZD1981
Mechanism of Action	CRTh2/DP2 antagonist Chemoattractant receptor-homologous molecule expressed on Th2 cells (CRTh2)/prostaglandin D2 (DP2) receptor antagonist http://iuphar-db.org/DATABASE/ObjectDisplayForward?familyId=58&objectId=339 http://www.ncbi.nlm.nih.gov/gene/11251
Overview	AZD1981 is a potent orally bio-available CRTh2 antagonist. CRTh2 is a G protein-coupled receptor (GPCR) that is activated by PGD_2 and several of its metabolites. CRTh2 is expressed on immune cells associated with the allergic response such as Th2 cells, eosinophils and basophils. In addition, CRTh2 has been shown to be abundantly expressed at both protein and mRNA level on epithelial cells in both the lung and gut. In pre-clinical studies, AZD1981 inhibited PGD_2 binding to human CRTh2 with an IC50 of 4 nM and similar potency was demonstrated in rat and mouse CRTh2 binding assays. The antagonist potency of AZD1981 has been assessed in a number of cell systems in which a response mediated by the human CRTh2 receptor can be evoked by PGD_2, DK-PGD_2 or 15-R-MePGD_2 and quantified using eosinophil shape change, CD11b expression, or chemotaxis. AZD1981 inhibited PGD_2 or DK-PGD_2-stimulated chemotaxis of human Th2 cells and eosinophils. AZD1981 reduces PGD_2-induced eosinophil mobilization in a guinea pig PD model. To achieve optimal exposure for in vivo studies in mice and rats the compound needs to be dosed 3 times a day. AZD1981 has been investigated in single and multiple ascending dose studies in healthy volunteers and in Phase 2 clinical trials of up to 12 weeks duration in asthma patients and 4 weeks duration in COPD patients.
Safety/Tolerability	Following oral administration of AZD1981, treatment-related findings associated with the kidney were seen in all pre-clinical toxicological species. In rats this is characterized by increased water consumption and increased kidney weights with non-adverse histopathological changes being seen after 26-weeks. In dogs, nephropathy was identified histopathologically after 4 weeks, however this occurred at the highest dose only (2000 mg/kg/day) and the effects were slight; the effects were not repeated following either 13 or 52 weeks of dosing, albeit at a lower dose level (1000 mg/kg/day). Findings related to the liver (evidence of Cytochrome P450 induction and increased plasma bilirubin levels), which were also considered to be associated with treatment with AZD1981, were considered to represent an adaptive response, rather than an injurious toxic insult. In early phase clinical studies, AZD1981 was shown to be well tolerated over the dose range studied (single oral doses up to 4000 mg; repeated doses of up to 2000 mg twice daily over 2 weeks). Treatment of asthma or COPD patients with AZD1981 tablets 1000 mg twice daily for 4 weeks was well tolerated. A small number of patients had slight transient elevations of ALT or AST levels without any concomitant increase in bilirubin. Treatment of asthma patients with AZD1981 at doses up to 400 mg twice daily for up to 12 weeks was well tolerated with an adverse event profile generally similar to placebo. In general, AZD1981 demonstrated no clinically relevant findings in clinical laboratory assessments, physical exam, ECG, or vital signs compared to placebo. A small percentage of patients treated with AZD1981 had notable elevations of ALT and AST values without notable increase in total bilirubin. Results suggest a dose-response relationship with the highest percentage of subjects having identified LFT abnormalities in the AZD1981 400 mg bid group. In all cases, transaminases returned to baseline after AZD1981 was stopped. However, the possibility that AZD1981 may be associated with an increased risk of liver injury cannot be excluded. In completed drug-drug interaction studies, AZD1981 increased the plasma exposure of ethinyl estradiol in female volunteers receiving a combined oral contraceptive (COC), and increased the plasma exposure of warfarin (CYP2C9 substrate) and pravastatin (OATP1B1 substrate). Plasma concentrations of midazolam (CYP3A4 substrate) were modestly decreased by AZD1981.

Additional Information	The predicted dose from SAD/MAD for AZD1981 to maintain clinically relevant systemic exposure in fed individuals was 80 mg BID and in fasted was 160 mg BID. Data from clinical studies with the tablet formulation suggests effective systemic exposure can be achieved at 50 mg BID in fasted asthmatics. In two Phase 2a studies in asthma patients, AZD1981 showed some evidence of treatment related changes in lung function and symptoms compared to placebo, an effect that seemed more apparent in atopic individuals receiving ICS therapy. In a 12 week Phase 2b dose finding study in atopic asthma patients on inhaled corticosteroid and long-acting beta agonist (ICS/LABA) therapy and in two Phase 2a studies conducted in patients with moderate to severe COPD, primary and/or secondary efficacy objectives were not met.
Suitable for and Exclusions	Reproductive toxicity studies support the inclusion of women of child-bearing potential in clinical studies, provided that pregnancy is prevented using a reliable form of contraceptive. Potentially clinically significant interactions with COCs, warfarin and pravastatin have been observed; therefore medication restrictions or additional monitoring may be warranted. Based on safety findings in clinical studies to date, liver function monitoring would need to be incorporated into future clinical development plans. There are currently no clinical data to support use in pediatric populations below 12 years of age, although existing preclinical data would support clinical studies in a pediatric population of > 5 years. Proposals for studies in ophthalmology or dermatology are not of interest.
Clinical Trials	http://clinicaltrials.gov/ct2/results?term=AZD1981
Publications	http://www.ncbi.nlm.nih.gov/pubmed?term=AZD1981